toxicity from infusion of FMCs. Two of eight evaluable patients had a complete response and four had a partial response, giving an overall response rate of 75%. Three patients are alive from 6 to 21 months after HSCT. One patient is well and two have chronic GVHD. Two patients showed no response at all.

Thus, FMCs may be successfully used for immune modulation and tissue repair.

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α-Mannan Can Induce Acute Pulmonary GvHD Dependent On Th17 Subsets

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Fungal infection is a serious complication after allogeneic hematopoietic stem cell transplantation but its impacts on graft-versus host disease (aGVHD) remains to be elucidated. α-mannan, one of the main components of fungal cell wall, induces Th17 responses, leading to the elimination of fungi. We therefore hypothesized that fungal infection could modulate GVHD by inducing Th17 responses. Lethally irradiated B6D2F1 (H-$2^{b/d}$) mice were injected with 4 x 10^6 BM and 4 x 10^6 T cells from MHC-mismatched B6 (H-2^b) donors on day 0. Mice were intraperitoneally injected with 20mg of α-mannan or diluent on day 1. GVHD was severe in mannan-treated allogeneic mice, with 16.7% survival by day30, whereas 83.3% of allogeneic controls survived this period (Table). Histopathologic examination showed significantly exacerbation of GVHD pathology, especially in the lung, of mannan-treated animals than in controls (Table).

A flowcytometric analysis of the spleen and thymus after BMT showed that administration of mannan did not alter donor cell engraftment.

We then evaluated the roles of Th17 in aGVHD of mannan-treated allogeneic models using IL-17-deficient mice as donors. Infusion of IL-17-/- T cells significantly improved GVHD clinical scores (3.5 ± 0.4 vs 5.5±0.3 at day14, P<.05), survival (62.5% vs 12.5% at day 30, $P < .05$) and pulmonary GVHD pathology scores (1.0±0.5 vs 7.0±1.0 at day21, $P < .05$) compared with those of mannan-treated controls.

These results suggest that mannan can exacerbate acute GVHD, mainly on pulmonary lesions.Th17 contribute to the development of acute pulmonary GVHD in this model, and that targeting Th17 may therefore represent a promising therapeutic strategy for treating acute pulmonary GVHD.

Table

Group	Clinical GVHD scores on day+14	Survivals on day+30 (%)	Pathology Scores		
			Lung	Liver	Intestine
TCD Diluent	1.1±0.8	100	0	0.3±0.4	0.7±0.4
TCD α-mannan	1.2±0.5	100	0	0.7±0.8	0.5±0.5
+T Diluent	3.6±0.7	83.3	1.5±0.7	2.5± 1.2	2.0± 0.8
+T α-mannan	5.7±0.5†	16.7*	7.0±1.0†	4.0± 1.8	2.5± 0.8

TCD: T cell-depleted BMT, +T: T cell-repleted BMT.
Data are expressed as mean ± SD.
* $P < 0.01$ vs control.
† P<0.05 vs control.

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Plasma ST2 Concentrations Predict Acute Gvhd Development and Non-Relapse Mortality

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Acute GVHD is the primary limitation of allogeneic HSCT. We have previously reported that plasma concentrations of suppressor of tumorigenicity 2 (ST2) at the onset of GVHD therapy predicted response at day (D) 28 and non-relapse mortality (NRM) at D180 after therapy initiation. We hypothesized that ST2 measured early in HSCT would predict GVHD occurrence by D100 and D180 NRM after HSCT.

We measured ST2 in plasma taken at D0, D14 and D21 after HSCT in a pilot set. ST2 concentrations at D14 were most different between patients who developed GVHD and those without GVHD, and were twice higher in patients receiving full intensity conditioning (FIC) compared to those receiving reduced intensity conditioning (RIC). We then measured ST2 concentrations at D14 in two independent sets: 1) 598 patients from the University of Michigan (UM), 69% receiving FIC (15% receiving TBI) and 31% receiving RIC HSCT, 2) 75 patients receiving unrelated, FIC (92% receiving TBI) HSCT from the Dana Farber Cancer Institute (DFCI). UM patients who developed GVHD were older and more likely to receive mismatched or unrelated donor HSCT. Median day of GVHD onset was D35 in FIC and D42 in RIC (p=0.08). DFCI patients who received sirolimus as GVHD prophylaxis were over-

Table 1
ST2 concentrations at D14 predict GVHD development by D100 and predict D180 NRM

	UM FIC (n = 414)		UM RIC (n = 184)		DFCI (n = 75)	
	Hazard Ratio (HR)	*P*-value	HR	*P*-value	HR	*P*-value
Age (55 and Over vs. Under 55)	1.5	0.01	0.8	0.4	0.1	0.02
Disease Status (High vs. Low risk)	1.0	0.99	1.8	0.02		n/a
Donor (Unrelated vs. Related)	1.9	<0.001	0.9	0.7		n/a
HLA match (Mismatched vs. Matched)	2.1	<0.001	1.0	0.9	2.7	0.09
ST2 Concentration (High vs. Low)*,†	1.5	0.004	1.3	0.3	2.0	0.08
Age	3.1	<0.001	0.7	0.4	0.7	0.5
Disease Status	1.1	0.6	2.7	0.02		n/a
Donor	1.5	0.1	1.1	0.8		n/a
HLA match	1.7	0.06	0.5	0.3	1.9	0.2
ST2 Concentration	2.8	<0.001	4.8	0.005	2.6	0.04

* Effect of ST2 calculated with regression models adjusting for age, disease status, donor, and HLA match.
† High defined as ST2 concentration >600 pg/mL for UM FIC, >300 pg/mL for UM RIC, >1660 pg/mL for DFCI.

represented in the no-GVHD group. As ST2 concentrations differed between conditioning intensities, we used 3 models for prediction using the median ST2 concentrations for UM FIC, UM RIC, and DFCI FIC as cutpoints.

In multivariate analysis including the age, disease status, donor source, and HLA match, high ST2 predicted the development of GVHD in UM FIC, and trended toward significance in the DFCI set (Table 1 Top). Patients with high ST2 at D14 were at increased risk of D180 NRM for all conditioning intensities, independent of the clinical characteristics (Table 1 Bottom). High ST2 was not associated with increased risk of relapse mortality 1 year after HSCT.

In conclusion, high ST2 early in HSCT identifies patients at high risk for acute GVHD and NRM following HSCT. This has therapeutic consequences including increased monitoring and potential preemptive interventions.

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Interim Analysis of a Phase II Trial of Montelukast for the Treatment of Bronchiolitis Obliterans Syndrome After HSCT Reveals Immunobiology of Disease

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Bronchiolitis obliterans syndrome (BOS) after allogeneic HSCT is associated with high mortality and unknown pathogenesis. We present interim results from a prospective phase II trial evaluating of montelukast for the treatment of BOS after HSCT and studying BOS biology. Montelukast interrupts cysteinyl leukotriene activity and may diminish homing of activated cells to bronchioles and fibrosis. Twenty-three patients have enrolled with stable or decreasing immunosuppression for 3 months prior and BOS diagnosed by modified NIH criteria; 2 were withdrawn, and 19 have completed primary endpoint. Participants ranged from 15-72 years, 13/23 female, most had moderate to severe disease with baseline FEV1 of 46% predicted (24-73), and median FEV1/VC 0.5 (0.29-0.78). Montelukast was well-tolerated and no patient required escalation of BOS-directed therapy during the evaluation period. All patients met criteria for treatment success (<15% decline in 6 months), with FEV1 either increased 5-13% of predicted (n=5), stable (n=7), or declined 5-13% (n=6). FEV1 slope of decline was generated using regression line of FEV1 value vs. days post-HSCT. At 6 months, slope was improved in 9 patients, stable in 9, declined in 1. Other manifestations of cGVHD showed: 5/8 GI GVHD improved and 3/8 stable; 5/10 liver cGVHD improved, 4/10 stable, 1 worse, using NIH consensus staging. Survival of the study cohort is 90% (19/21); 2 year survival is 84% (10/12), twice published data (44%). Bronchoalveolar lavage (BAL) from in non-infected patients at baseline revealed cysteinyl leukotriene receptor expression on CD4 and CD8 T cells, granulocytes, and eosinophils, thereby potentially implicating these populations in BOS biology. While blood leukotriene receptor expression on CD4 cells was similar to normal donors, CD4 proportion was significantly reduced in BOS patients ($P < 0.01$). Other blood receptor levels of these populations were similar between normal donors and controls, although CD8 T cells trended toward decreased receptor expression after treatment at 6 months and decreased proportion of CD8 T cells at 2 years ($p<0.04$). B cells were absent in BAL while present in blood. These data suggest that: 1) montelukast is a safe and effective therapy for BOS after allogeneic HSCT; 2) T cells, granulocytes, and eosinophils (though not B cells) were associated with BOS in BAL; and 3) cysteinyl leukotrienes may be a point of regulation in the progression of BOS after HSCT.

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Lower Uric Acid Level At the Time of Allogeneic Hematopoietic Cell Transplantation (HCT) Is Protective Against Acute Graft-Vs-Host-Disease

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Acute graft-versus-host disease (aGVHD) is primarily a T-cell mediated process. Uric acid released from dying cells acts as a danger signal that alerts the immune system to cell death and promotes cytotoxic T cell responses. Elimination of uric acid in mouse models reduces this immune response. We hypothesized that lower serum uric acid levels at the time of transplant may decrease the incidence of aGVHD. Through record review, we recorded serum uric acid levels from day -7 through day +6 from 43 historical control patients who received myeloablative HCT (MRD, n=32; MUD, n=11) at the Massachusetts General Hospital between 2007 and 2010, these patients received standard allopurinol. We also obtained uric acid levels from 23 consecutive patients (19-59 years) with hematologic malignancies in complete remission (AML, n=13; ALL, n=8; MDS, n=1; MPD, n=1) who were treated in a pilot trial using rasburicase as part of a myeloablative conditioning regimen, followed by GCSF-mobilized HLA-matched (MRD, n=18; MUD, n=5) peripheral blood HCT. Urate oxidase (Rasburicase) was administered beginning on the first day of conditioning at a dose of 0.20 mg/kg IV daily for 5 days starting from day -7. GVHD prophylaxis for all patients consisted of cyclosporine or tacrolimus/MTX for MRD transplants and tacrolimus/MTX/ +/-ATG for MUD transplants. Out of the control group, patients who developed aGVHD (grade 2+) had a similar mean serum uric acid level over all days (2.82 mg/dl) compared to patients who did not have aGVHD (2.86 mg/dl,